



Nutrition and Cognitive Development: The Influence of Nutrient Synergy

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Cheatham Nutrition & Cognition Laboratory



- Developmental cognitive neuroscientist (developmental psychologist)
- How nutrition affects brain development and function
- From preconception to birth to old age, nutrition is central to brain function.



Disclosures

I have no relevant disclosures.

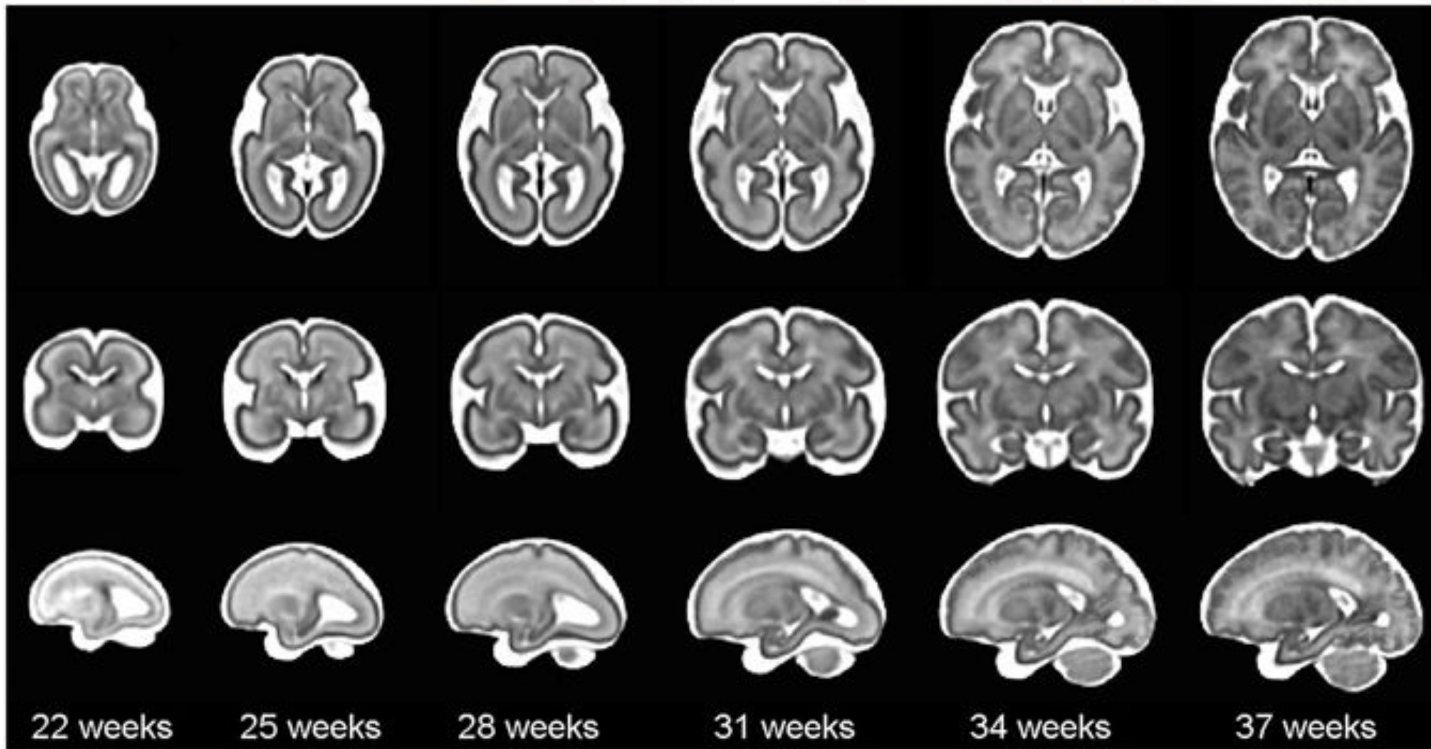


Objectives

- Detail early brain development
- Understand the importance of cognition
- Learn about specific nutrients' effects on brain
- Understand the synergy among nutrients



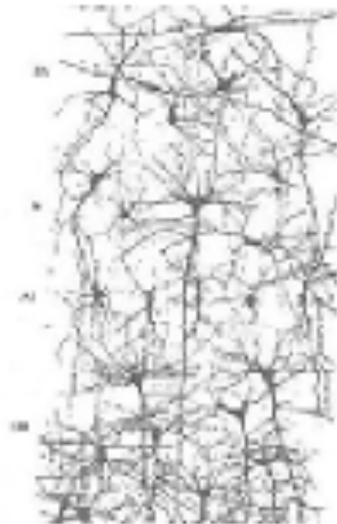
Fetal Brain Development



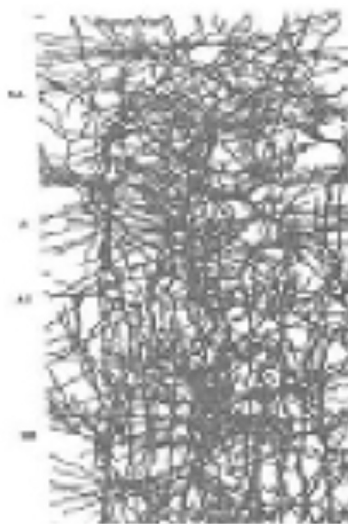
Postnatal Brain Development



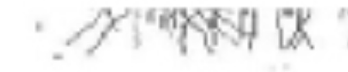
NEWBORN



3 MONTHS



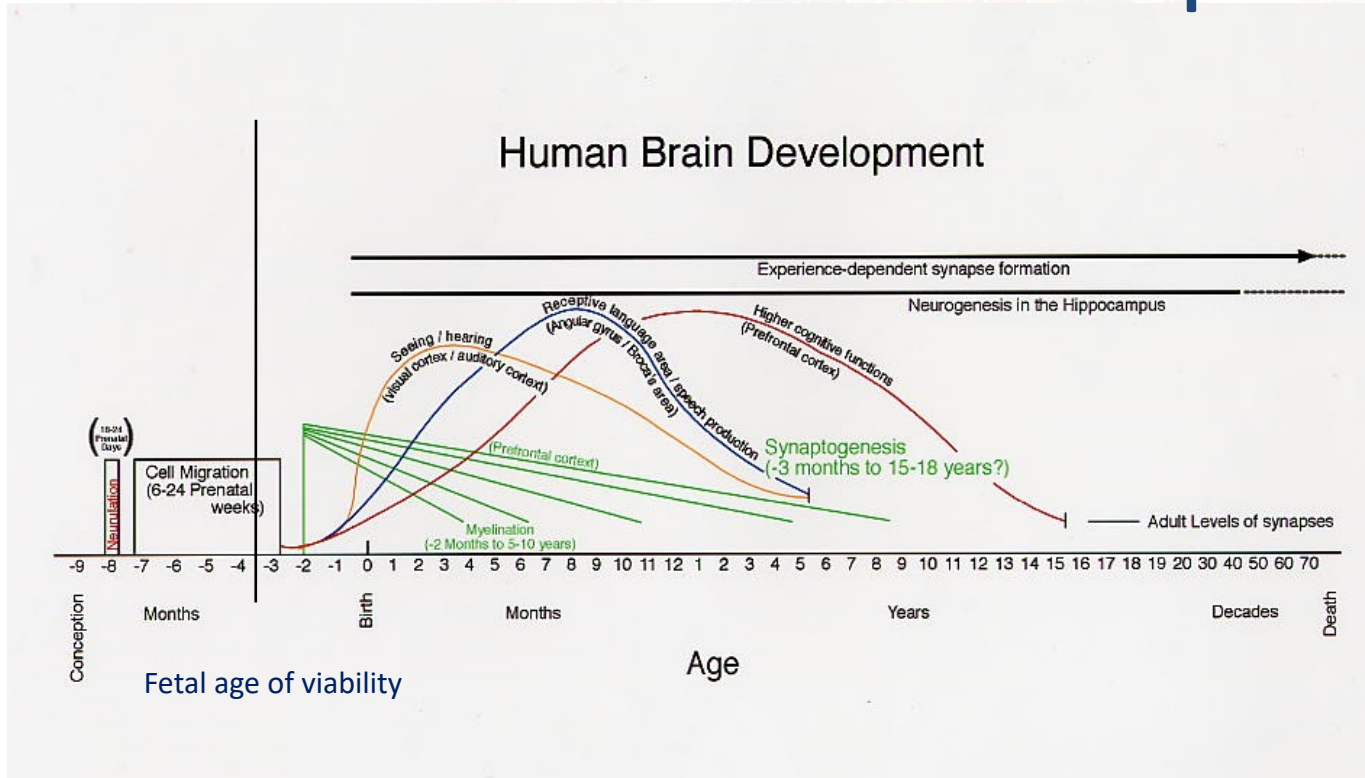
24 MONTHS



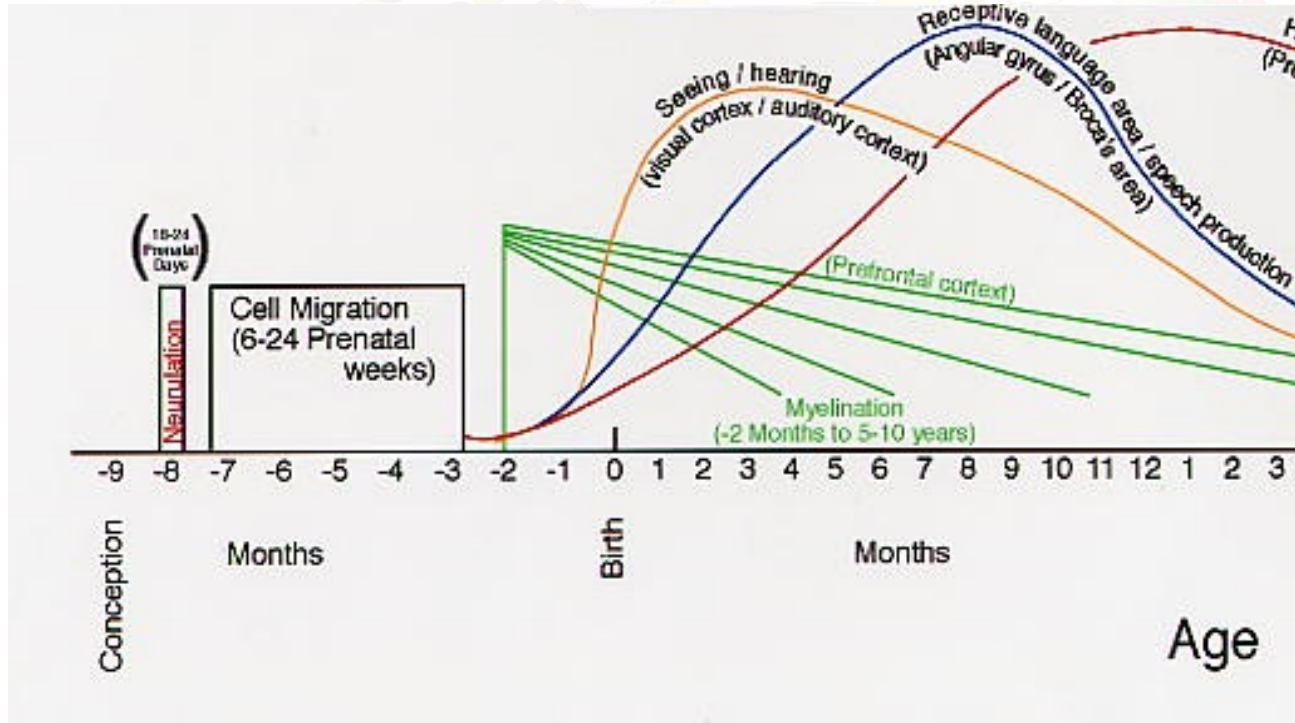
6 YEARS



Sensitive Periods of Development

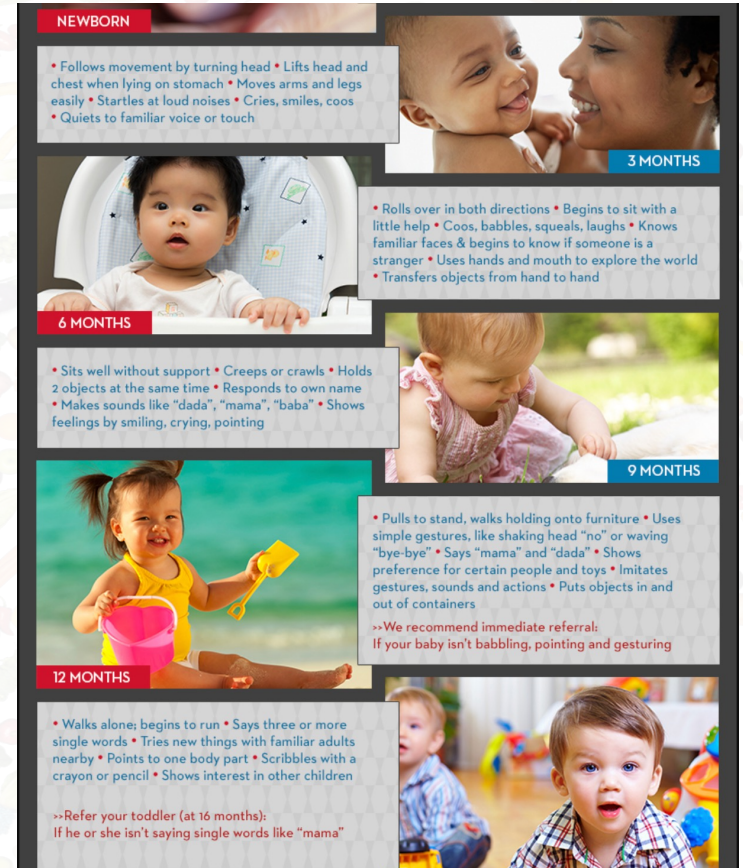


The First 1000 Days



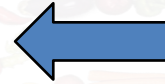
What is Cognition?

- Sigelman & Rider: “the activity of knowing and the process through which knowledge is acquired and problems are solved.”
 - Processing speed, memory, attention, problem-solving, reasoning
- All cognitive abilities rely on the brain.
- Early milestones are related to future earnings and contribution to society.
 - Early detection of issues allow intervention.



<https://helpmegrowmn.org/cs/fragments/hmgheader/images/milestones-infographic.jpg>

The Influence of Nutrition



- Gasoline
- Oil
- Brake Fluid
- Antifreeze



- Vitamins
- Minerals
- Glucose
- Bioactives

Synergistic Activity of Nutrients

- Nutrients do not appear in isolation.
 - Must study effects of whole foods.

Why Whole Foods?



Why Whole Foods?



Amount per 1 cup, sliced (165g)

Calorie Information		
Amounts Per Selected Serving		%DV
Calories	137 (448 kJ)	8%
From Carbohydrate	131 (423 kJ)	
From Fat	3.7 (15.9 kJ)	
From Protein	2.8 (11.7 kJ)	
From Alcohol	0.0 (0.0 kJ)	

Carbohydrates		
Amounts Per Selected Serving		%DV
Total Carbohydrate	28.1 g	9%
Dietary Fiber	3.0 g	12%
Sugar	24.4 g	

Fats & Fatty Acids		
Amounts Per Selected Serving		%DV
Total Fat	0.4 g	1%
Saturated Fat	0.1 g	1%
Monounsaturated Fat	0.2 g	
Polyunsaturated Fat	0.1 g	
Total trans fatty acids	—	
Total trans-monounsaturated fatty acids	—	
Total trans-polyunsaturated fatty acids	—	
Total Omega-3 fatty acids	81.1 mg	
Total Omega-6 fatty acids	23.1 mg	

Learn more about these fatty acids and their equivalent names.

Other		
Amounts Per Selected Serving		%DV
Alcohol	0.0 g	
Water	135 g	
Ash	0.6 g	
Daffoine	0.0 mg	
Theobromine	0.0 mg	

Minerals		
Amounts Per Selected Serving		%DV
Calcium	16.6 mg	2%
Iron	0.2 mg	1%
Magnesium	14.8 mg	4%
Phosphorus	16.3 mg	2%
Potassium	257 mg	3%
Sodium	3.3 mg	0%
Zinc	0.1 mg	0%
Copper	0.2 mg	3%
Manganese	0.0 mg	2%
Selenium	1.0 mg	1%
Fluoride	—	

Vitamins		
Amounts Per Selected Serving		%DV
Vitamin A	1282 IU	25%
Vitamin C	45.7 mg	75%
Vitamin D	—	
Vitamin E (Alpha-Tocopherol)	1.0 mg	8%
Vitamin K	6.9 mcg	9%
Thiamin	0.1 mg	8%
Riboflavin	0.1 mg	8%
Niacin	1.0 mg	9%
Vitamin B6	0.2 mg	11%
Folate	23.1 mcg	3%
Vitamin B12	0.0 mcg	0%
Pantoic Acid	0.3 mg	3%
Choline	12.9 mg	
Beta-ne	—	

Sterols		
Amounts Per Selected Serving		%DV
Cholesterol	0.0 mg	0%
Phytosterols	—	

Protein & Amino Acids		
Amounts Per Selected Serving		%DV
Protein	0.8 g	2%

or

Vitamin C

<http://nutritiondata.self.com/facts/fruits-and-fruit-juices/1952/2>

Synergistic Activity of Nutrients

- Nutrients do not appear in isolation.
 - Must study effects of whole foods.
- Most likely synergistic activity
 - Food matrix allows gradual uptake.
 - Nutrients support absorption of other nutrients.
 - Naturally-occurring nutrients work with body.
- Beginning to research interactions:
 - Does a given nutrient have a better effect when considered in partnership with another nutrient?

New Focus of Our Research

- Neuroscience:
 - Neurons that wire together, fire together.
- Nutrition:
 - Nutrients that lurk together, work together.

Human Milk Composition

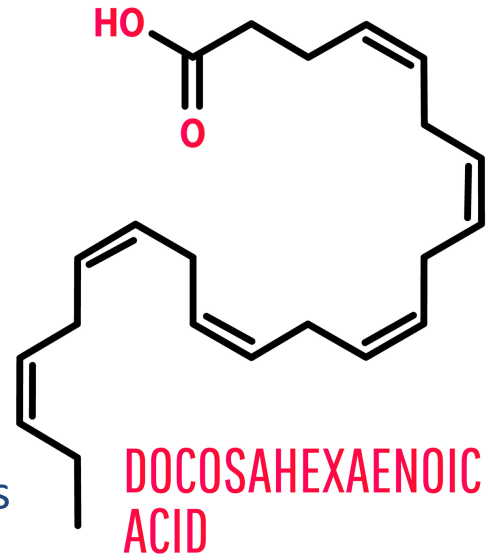
- Perfect food for human infants
 - Designed for human needs
- Other components include:
 - Hormones and growth factors
 - Oligosaccharides
 - ~800 strains of bacteria
 - Antibodies
 - Breast-specific macrophages
 - Stem cells and epithelial lactocytes
 - Etc.

Nutrient (per 4 oz)	
Niacin (mg)	0.4
Riboflavin (mg)	0.1
B12 (mcg)	0.1
Pantothenic Acid (mg)	0.5
Vitamin A (IU)	522
Thiamin (mg)	0.04
Pyridoxine (mg) aka B6	0.01
Folate (mcg)	18.8
Vitamin D (IU)	9.8
Vitamin E (mg)	0.2
Lutein (mcg)	2.16
Choline (mg)	39.4
Docosahexaenoic Acid (mg)	1.32

USDA National Nutrient Database for Standard Reference, R23 (2010)

What is DHA?

- Docosahexaenoic acid (DHA; 22:6n-3)
 - Also known as n-3 or omega-3 fatty acid
- Makes up 17% of brain total fatty acids
- Naturally occurring in fatty fish and eggs
- Biologically important
 - Component of neural membranes & synaptic vesicles
 - Increases the fluidity of synaptic transfer
- Endogenous synthesis of DHA is not sufficient for brain development
 - Fetus and neonate depend on maternal stores



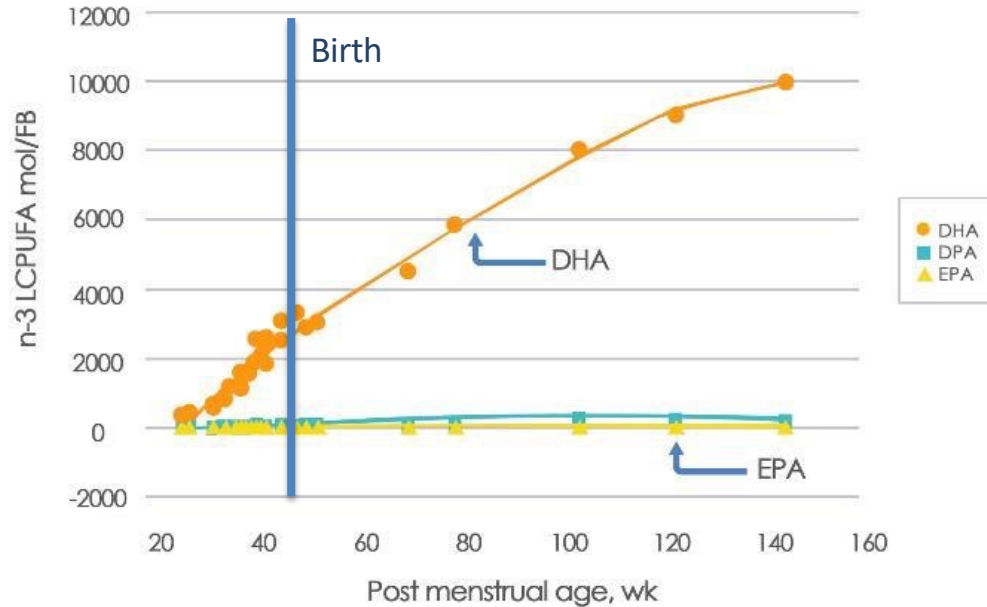
DHA Mechanisms of Action



Photo credit: whitehouse © 123RF.com

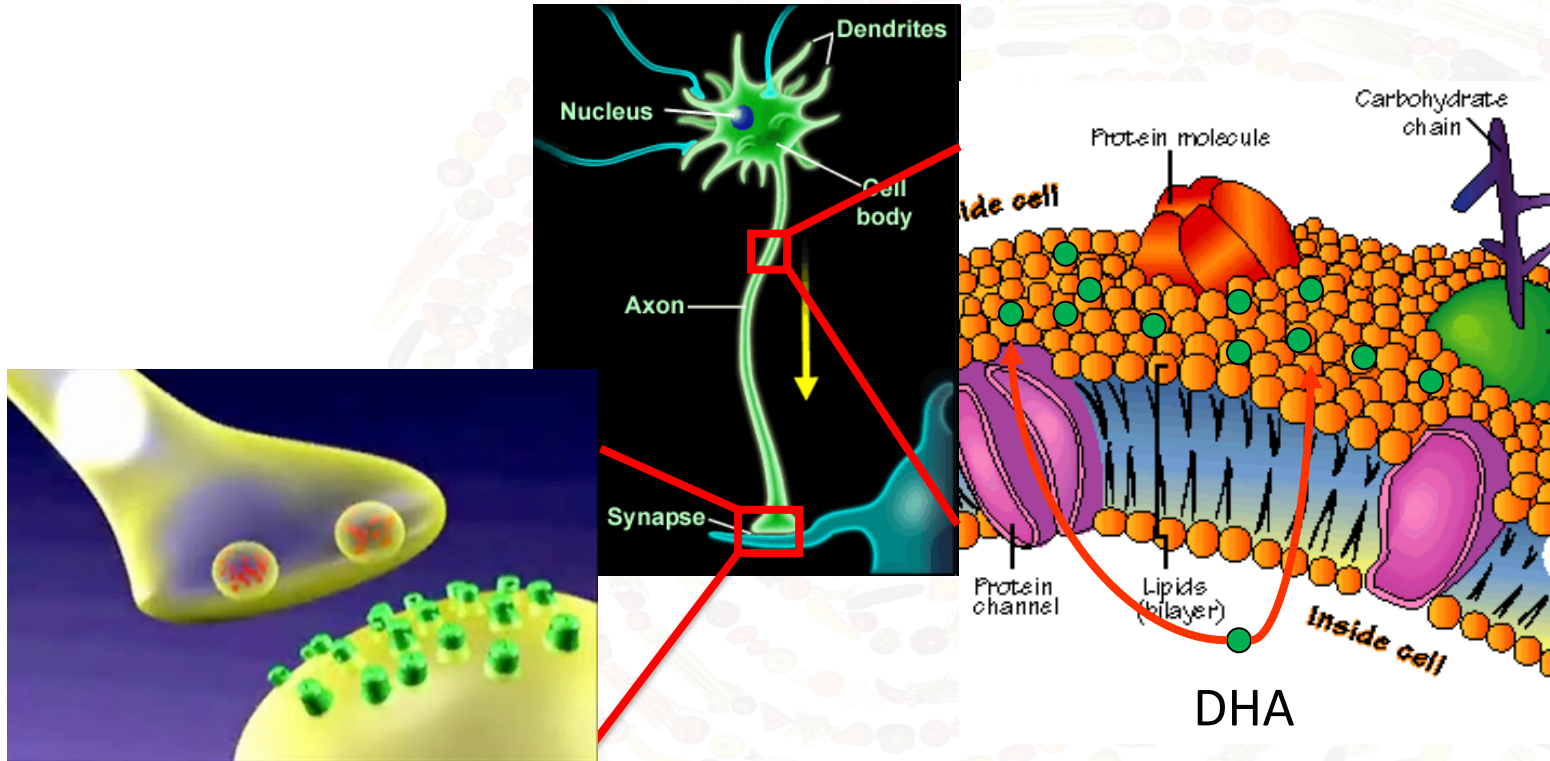
- Signal processing (Crawford et al., 2013)
- Needed for glutamatergic, serotonergic (Tang et al., 2016), and dopaminergic (Sugasini & Lokesh, 2015) neurotransmission
- Integral to long-term potentiation (LTP) in the hippocampus (Kavraal et al., 2012)

DHA Accumulation in the Brain



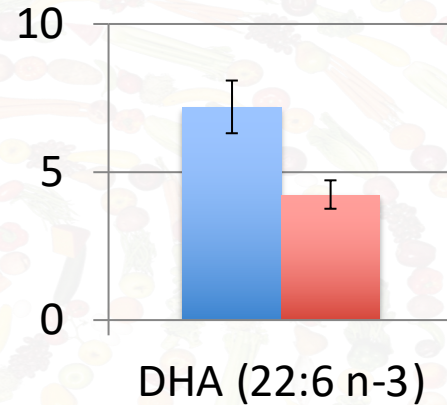
Martinez 1992

DHA in Neural Membranes



Human Milk Study

- Enrolled 200 breastfeeding dyads
- Milk samples at 3 months of age
 - Assayed for DHA
- Recognition memory at 6 months
 - Electrophysiology
 - Event-related potentials (ERP)
- Grouped by high and low DHA milk content





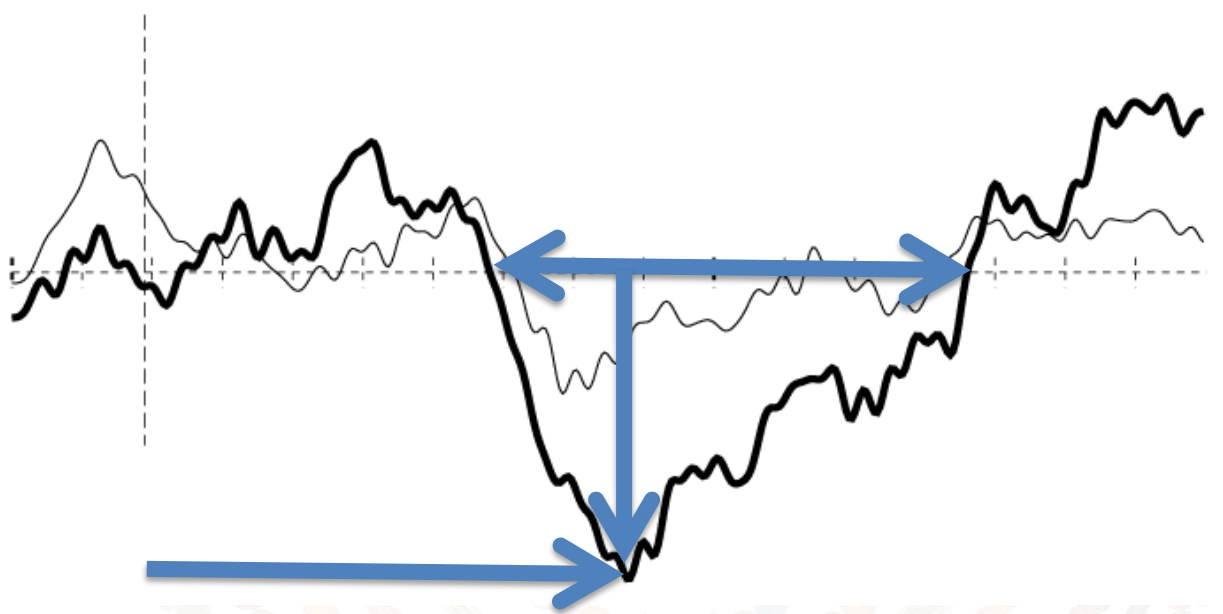
First Cheatham Lab Participant

Photo Credit: Jon C. Lakey/Salisbury Post

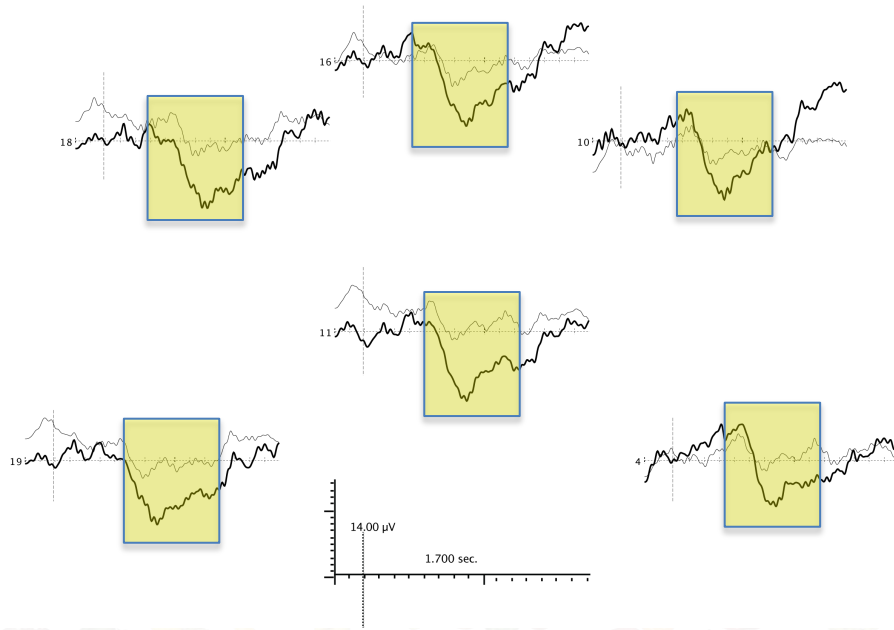
Recognition Memory Oddball Paradigm



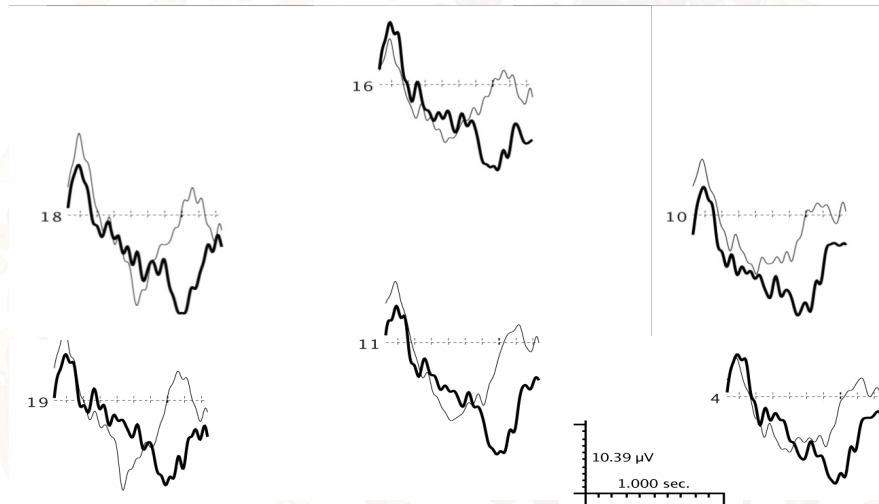
ERP Waveform: Novel vs. Familiar



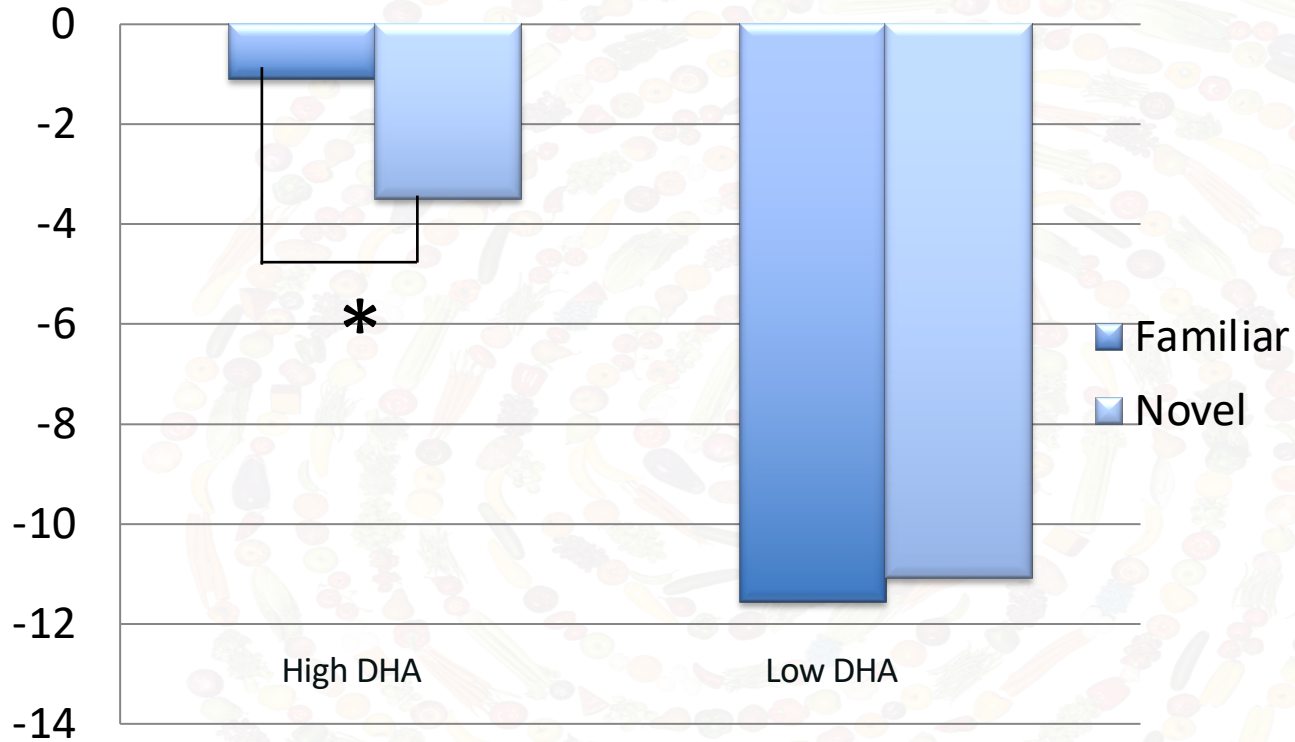
Novel vs. Familiar High DHA Content in Milk



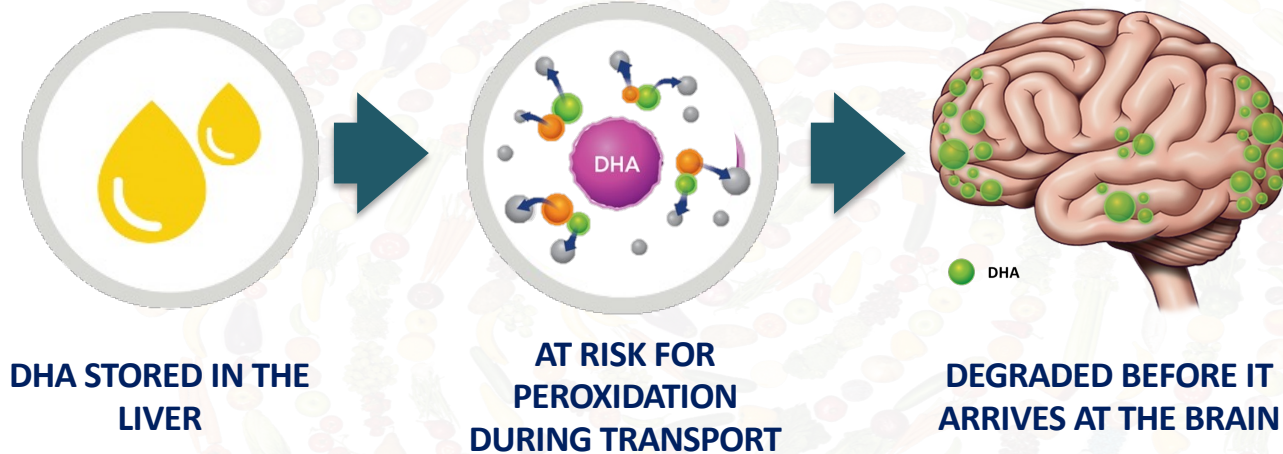
Novel vs. Familiar Low DHA Content in Milk



ERP Results: Novel vs. Familiar



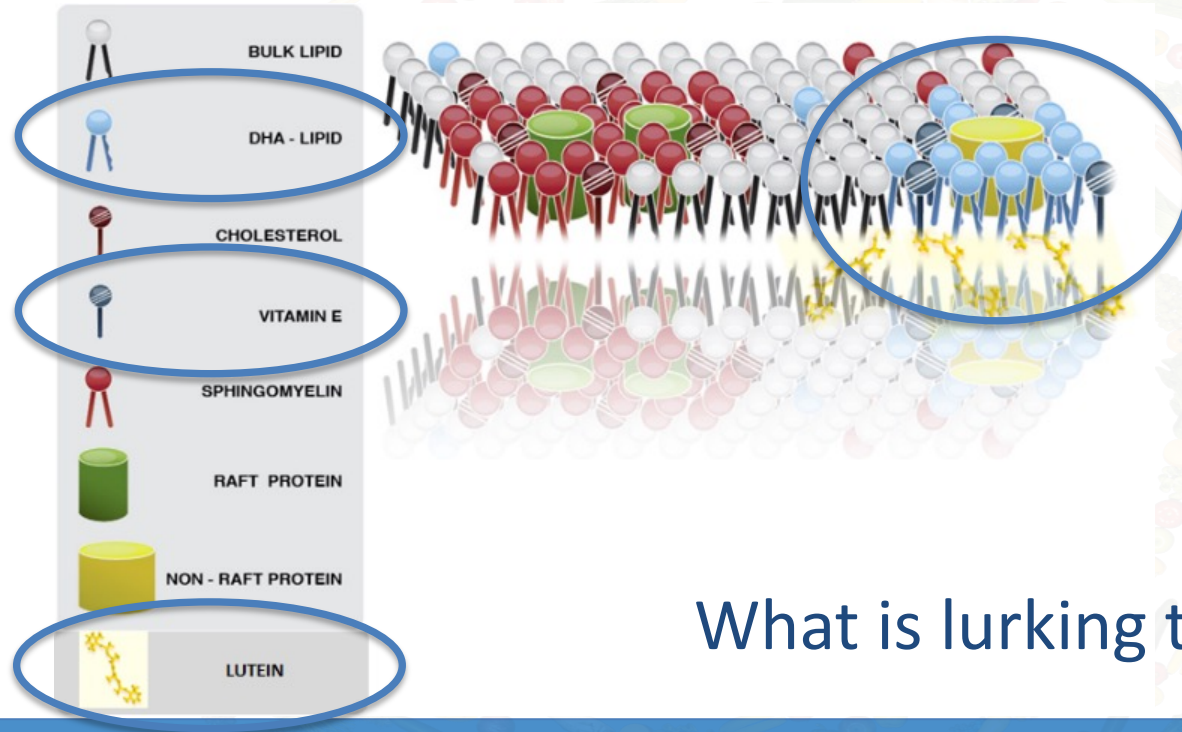
The Challenge That DHA Faces



What is Peroxidation of DHA?

- DHA is unsaturated
 - 6 double bonds = high susceptibility to oxidative damage
- Peroxidation is oxidative degradation of DHA by free radicals that results in peroxide.
- Oxidation is the removal of an electron
 - Produces a free radical (Reactive Oxygen Species, ROS)
 - ROS cause damage as they scavenge for an electron

Co-Localization of Nutrients



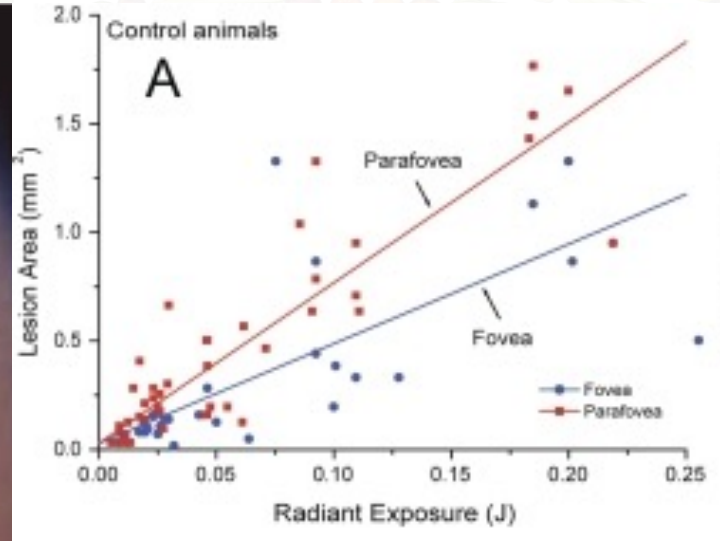
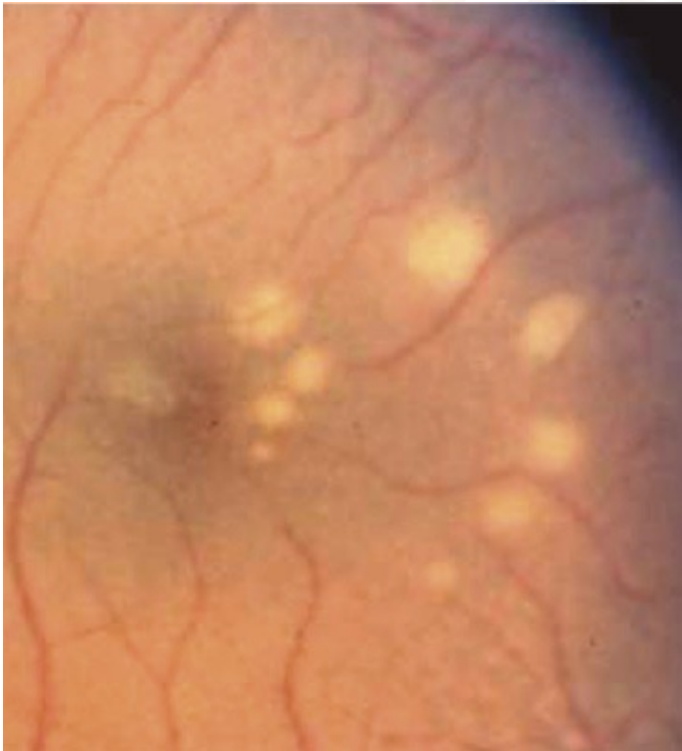
What is lurking together?

Lutein

- Carotenoid
- Essential
- Found in leafy greens and eggs
- Deposited directly into the retina
- Needed to block harmful blue light
- Antioxidant protection for the retina



Fovea Damage from Blue-Light

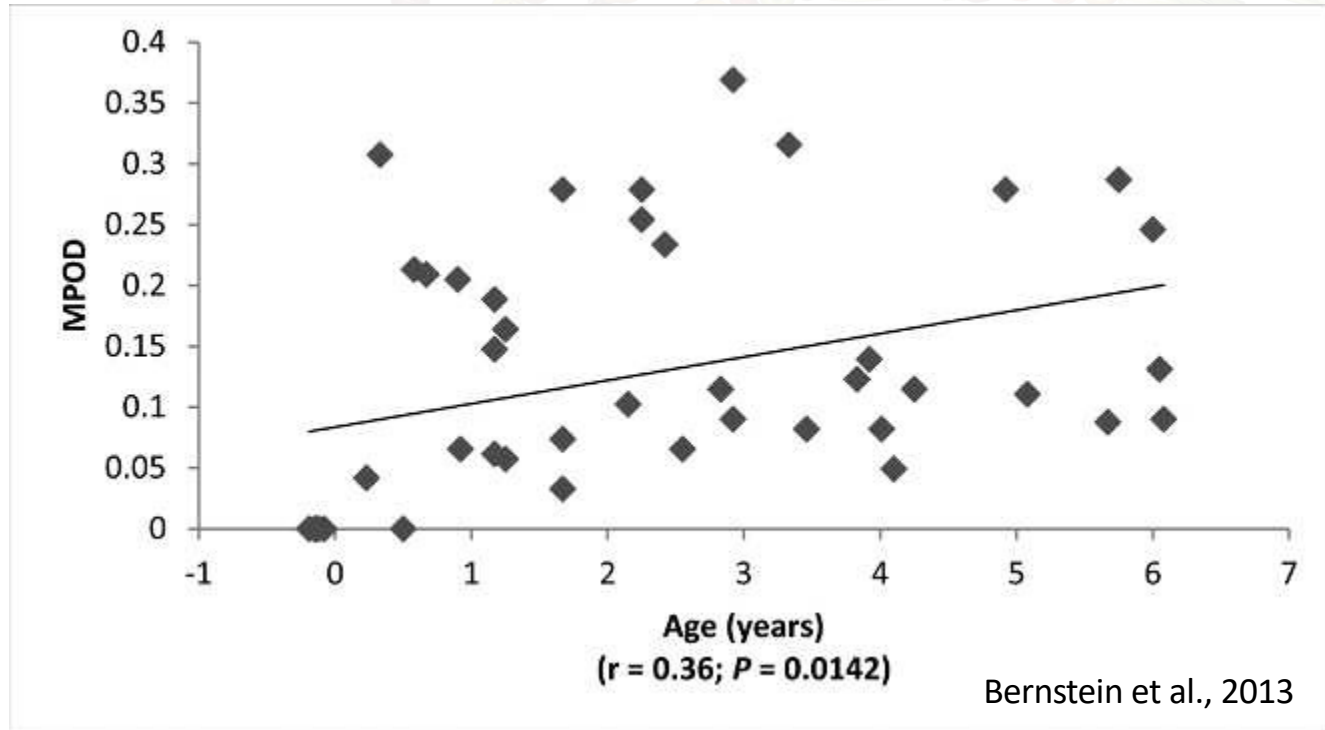


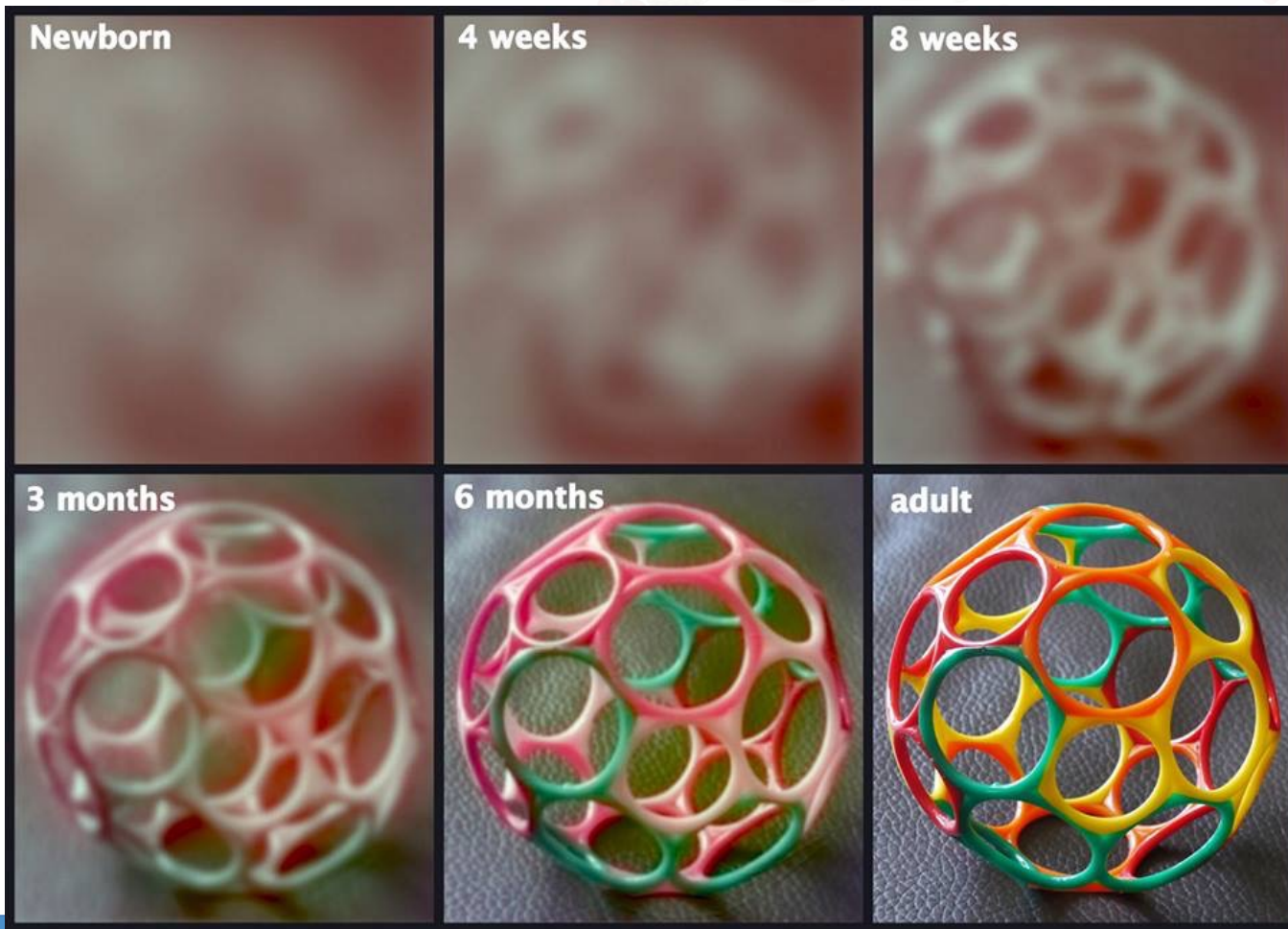
Barker et al, 2011 AJCN

Macular Degeneration



Macular Development





Newborn

4 weeks

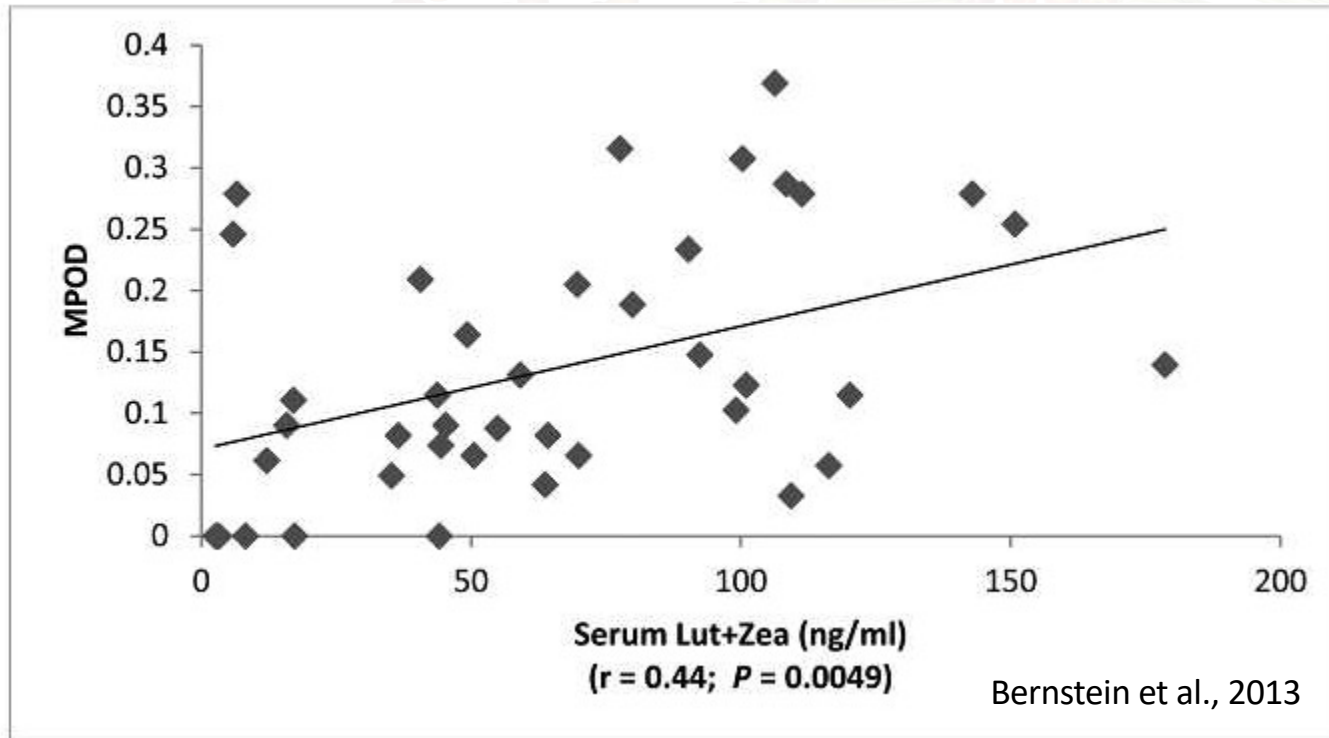
8 weeks

3 months

6 months

adult

Macular Development & Lutein

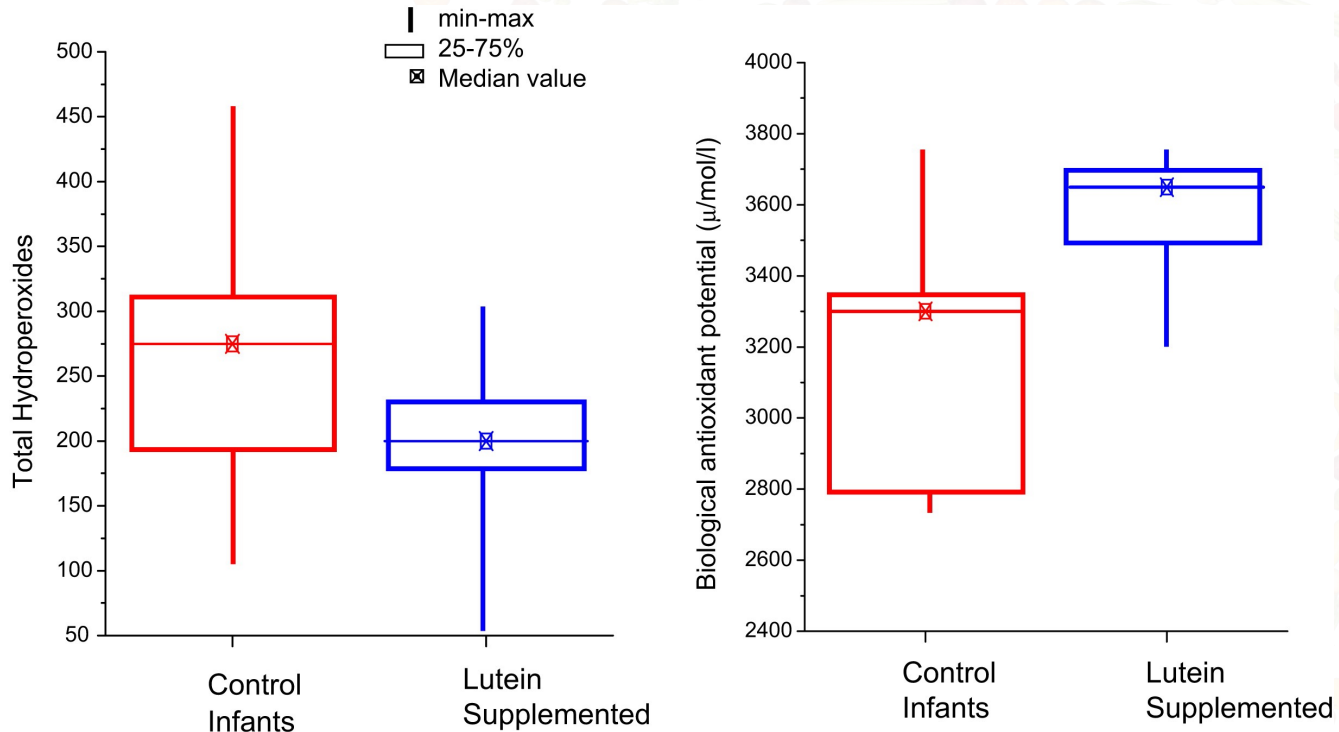


DHA and Visual Development

- Visual acuity
 - DHA is concentrated at the retina.
 - Evidence of improved acuity with supplementation
 - In infants born preterm (prenatal effects) and in 60% of trials with fullterms
 - and if measured by electrophysiology (SanGiovanni et al., 2000)
 - DHA may improve acuity transiently (4 months).
 - Confers a cognitive advantage to see more clearly sooner.
 - Need to get DHA from liver to brain without damage.

Lutein Protects DHA from Peroxidation

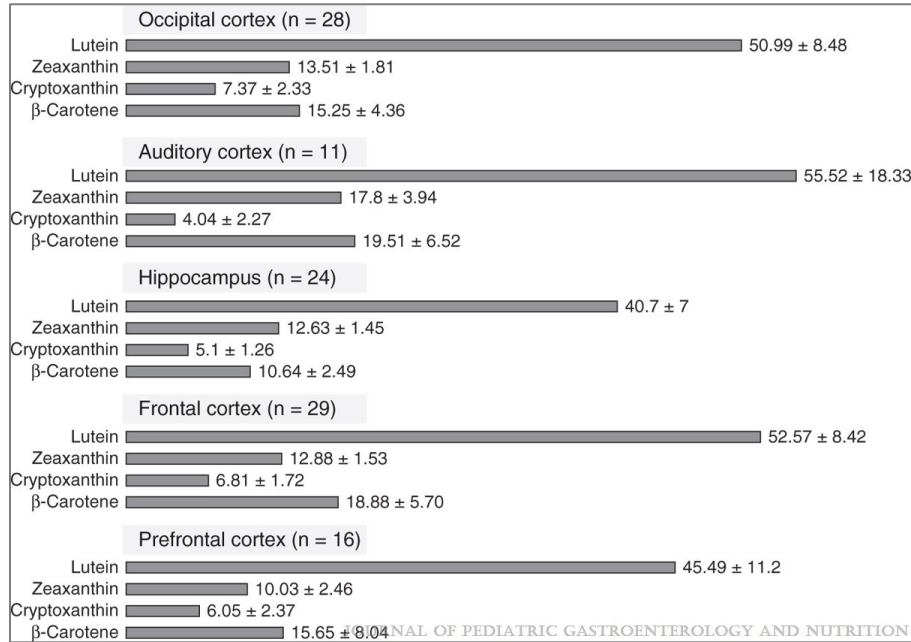
Lien & Hammond, 2011 adapted from Peronnee et al., 2010



Lutein in Brain

- Deposited in areas that subserve senses, memory, higher order cognition (Vishwanathan et al., 2014)

FIGURE 1



[Lutein and Preterm Infants With Decreased Concentrations of Brain Carotenoids](#)

Vishwanathan, Rohini; Kuchan, Matthew J.; Sen, Sarbattama; Johnson, Elizabeth J.

Journal of Pediatric Gastroenterology and Nutrition 59(5):659-665, November 2014.

doi: 10.1097/MPG.0000000000000389

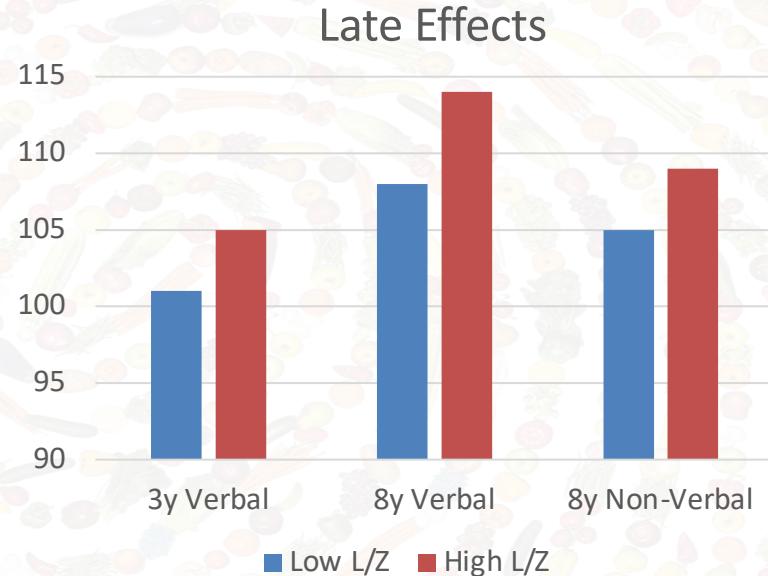
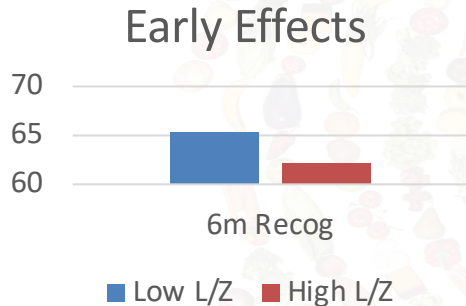
Distribution of carotenoids in the 5 brain regions analyzed. The difference between lutein and all other carotenoids (mean ± standard error of mean) was statistically significant in all regions (P < 0.05), except in the auditory cortex where the difference between lutein and β-carotene was marginally significant (P = 0.074, repeated measures analysis of variance).

Lutein in Brain

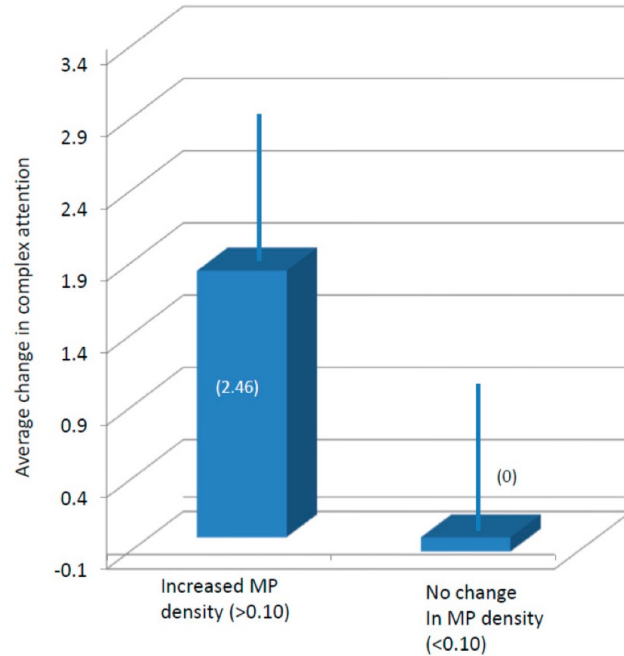
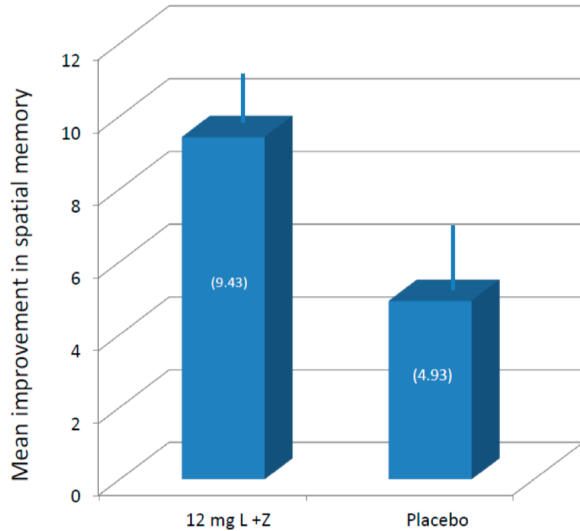
- Deposited in areas that subserve senses, memory, higher order cognition (Vishwanathan et al., 2014)
 - Assume action related to these functions
- Infants have twice the brain lutein of adults
 - (Johnson et al., 2013; Vishwanathan et al., 2014)
 - Accounts for over 50% of total brain carotenoids
 - Assume because lutein is needed during brain development
- More studies with adults than children at this point
 - Reviewers concluded lutein improves brain health (Yagi et al., 2021) and prevents cognitive decline (Li et al., 2021) in older adults .

Cognitive Effects of Maternal Intake (Lutein/Zeaxanthin)

- Maternal intake in first trimester related to mid-childhood cognitive abilities (Mahmassani et al., 2021)

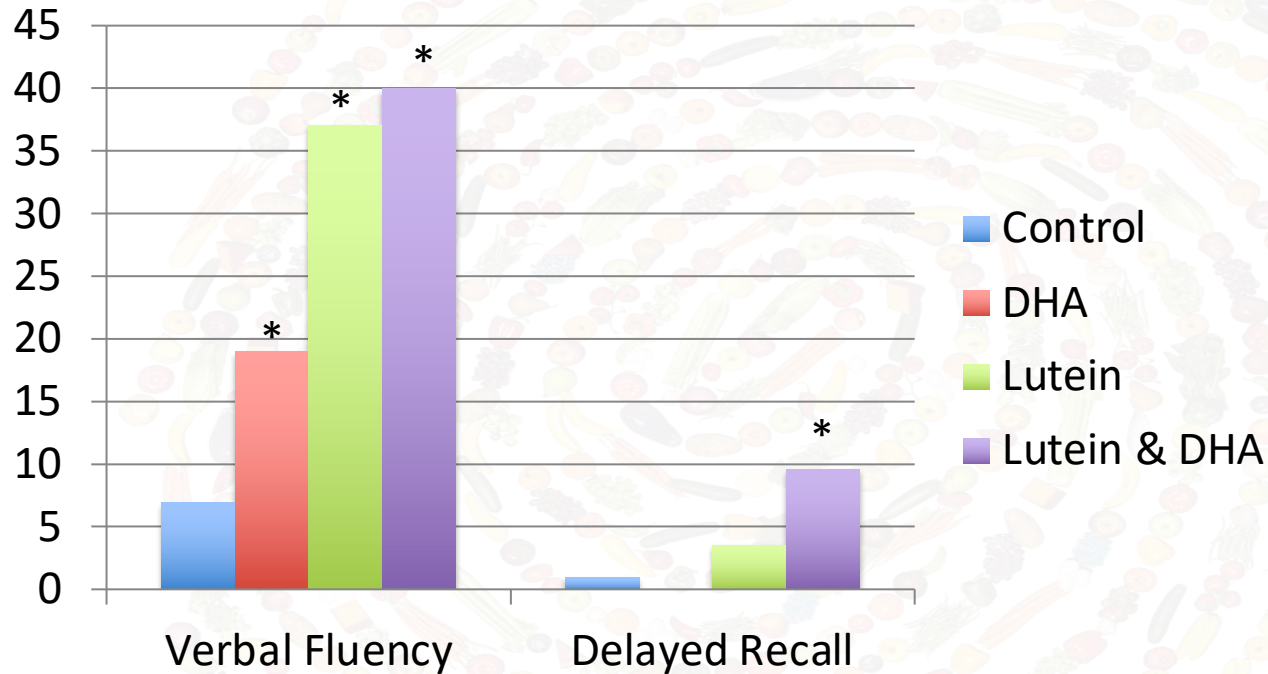


Lutein & Cognition



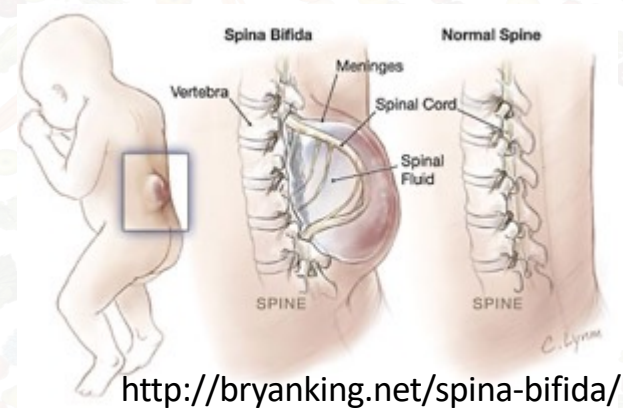
Renzi-Hammond et al., 2017

Synergy of Lutein & DHA



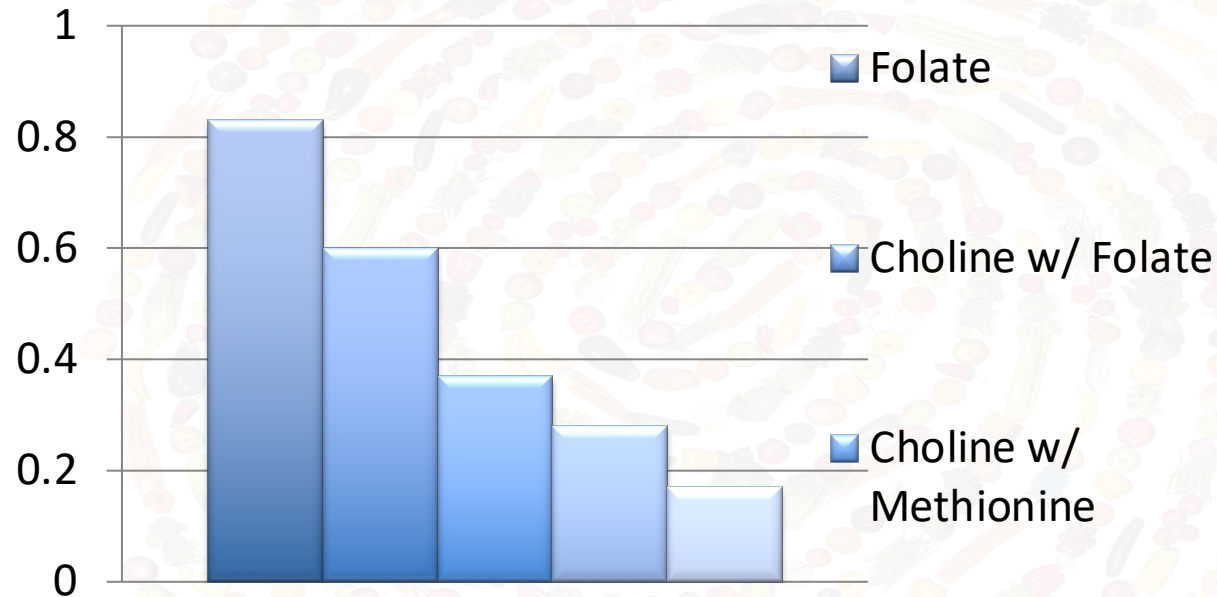
Folate

- Important at conception
 - Need to insure sufficiency preconception
- Needed for neural tube development
 - 1st 4 weeks gestation
- Evidence for importance of choline
 - Shaw et al., 2008



Risk of Neural Tube Disorders: Preconception Nutrient Intake

Odds ratio for NTDs given intake in the highest quartiles for these nutrients



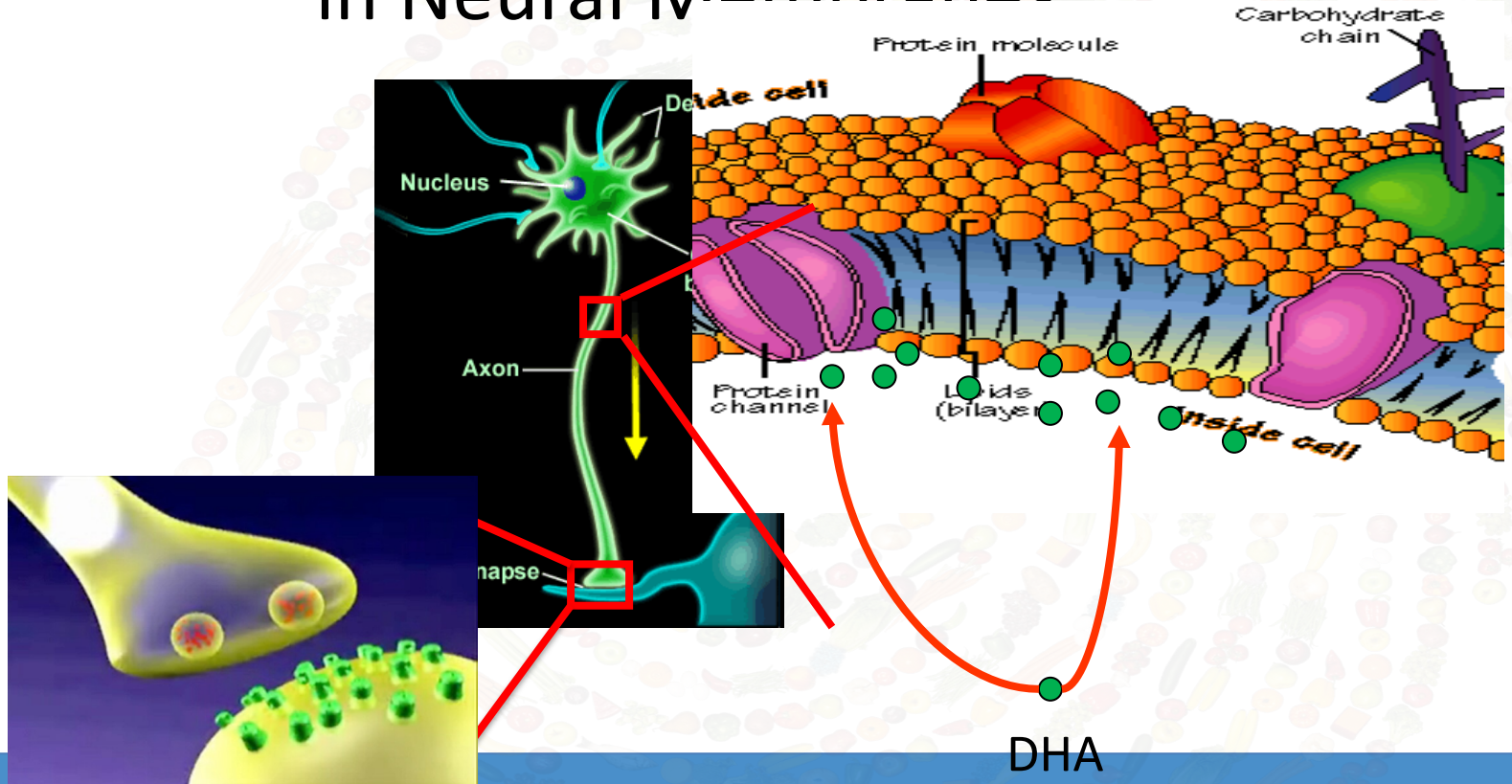
Shaw, Carmichael, Yang, Selvin, & Schaffer 2004

Choline

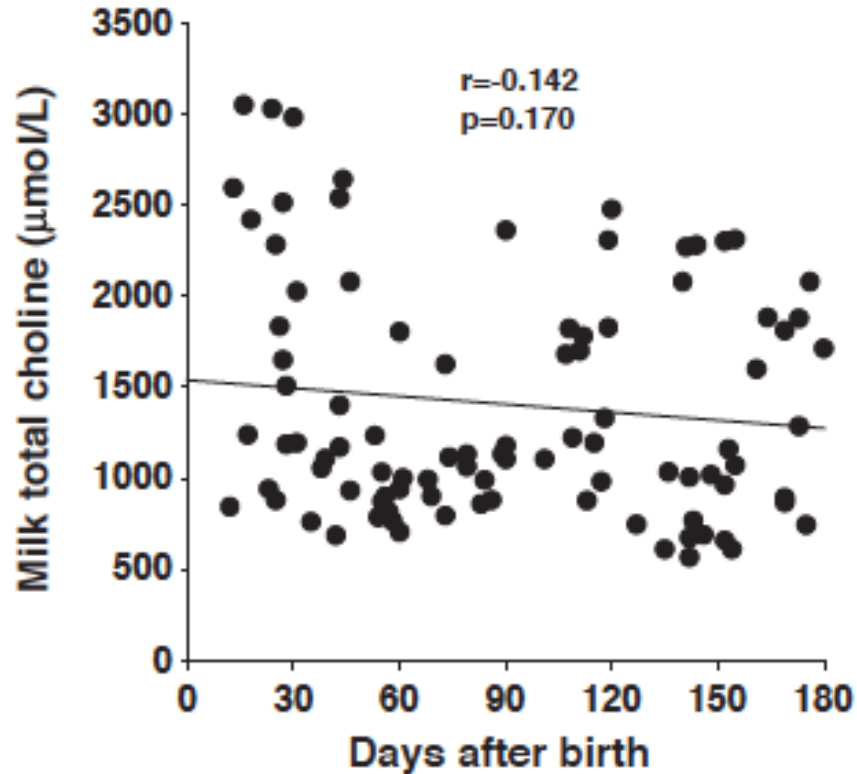
- Added as essential by FDA in 1998
- Found in eggs, shrimp, scallops, meat, nuts
- Animal research has shown prenatal (maternal) choline related to memory.
- Needed to release DHA from liver
- Methyl-donor
- Neurotransmitter (Ach)
- Structural (PtdCh + DHA)



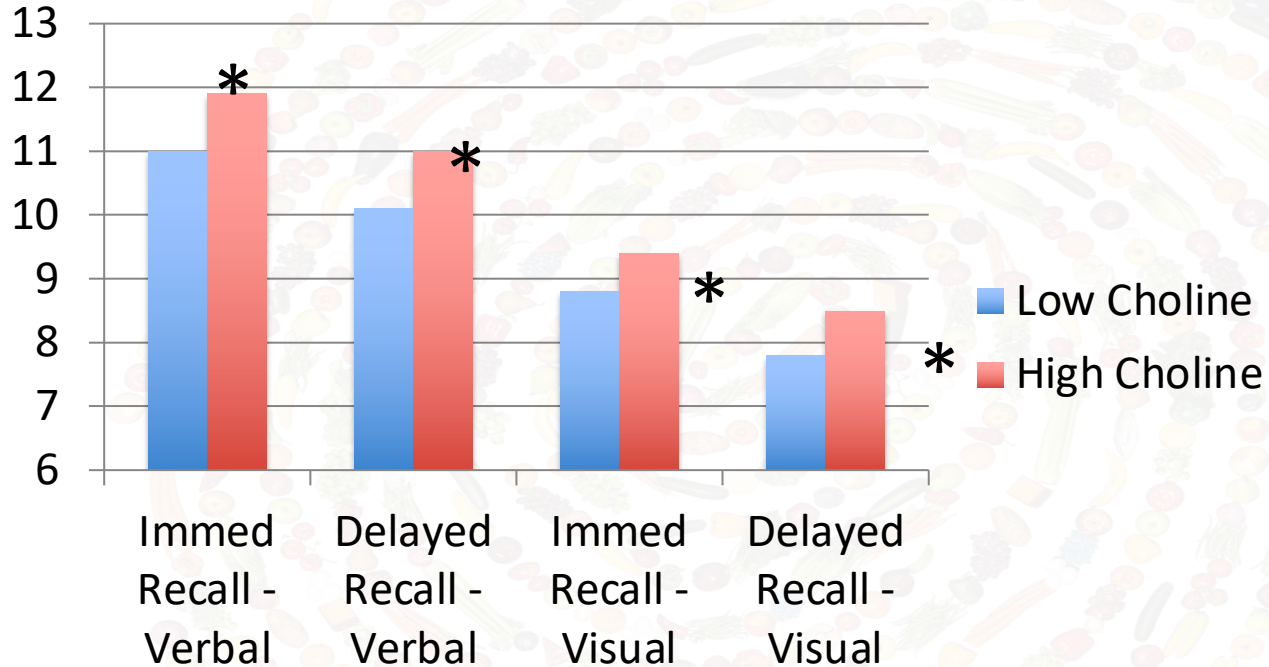
DHA & Choline in Neural Membranes



Choline in Human Milk

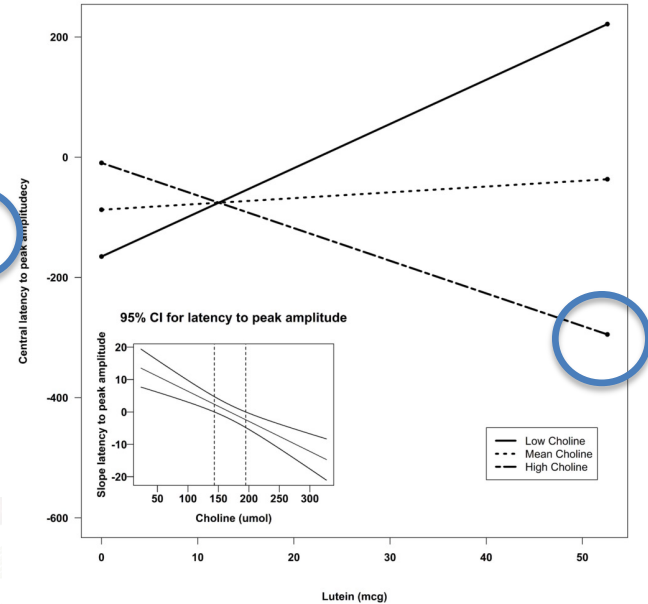
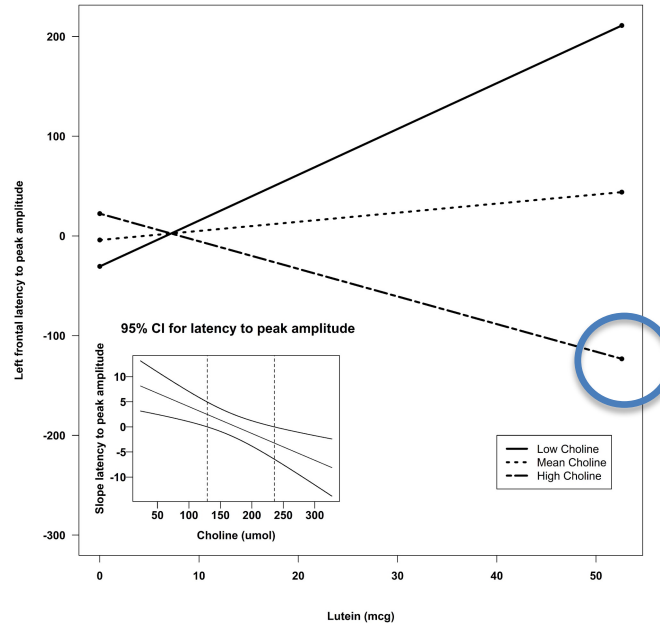


Choline & Cognition



Synergy of Lutein & Choline

- Human milk lutein & choline related to 6m recognition memory (Cheatham & Sheppard, 2015).



Take Home Points

- Cognitive development is an important indicator of future contributions to society.
 - Pediatricians should track milestone development.
 - Early interventions can make a difference.
- DHA is important for infant brain function.
- Ensuring that lutein and choline are present will prevent oxidation of DHA and preserve functions subserved by DHA.
- Single nutrient supplementation should be carefully considered.
- Nutrients work better as a team.



The Cheatham Nutrition & Cognition Team

THANK YOU...

All families that participate in research around the world

- Stevie Ray Wunder
- Patricia J. Bauer, Ph.D.
- Megan R. Gunnar, Ph.D.
- Michael K. Georgieff, M.D., Ph.D.
- Charles A. Nelson, Ph.D
- Steven Zeisel, M.D., Ph.D.
- J. Steven Reznick, Ph.D.
- A myriad of undergrads and grad students
- Funding agencies: NSF, NIH, CNBD, URC, CNRU, NRI, NORC
- Abbott Nutrition for the invitation

n-6/n-3 Ratio Papers



Omega-6 to omega-3 fatty acid ratio and higher-order cognitive functions in 7- to 9-y-olds: a cross-sectional study

Kelly W Sheppard and, Carol L Cheatham

The American Journal of Clinical Nutrition, Volume 98, Issue 3, September 2013, Pages 659–667, <https://doi-org.libproxy.lib.unc.edu/10.3945/ajcn.113.058719>

Executive functions and the ω -6-to- ω -3 fatty acid ratio: a cross-sectional study

Kelly W Sheppard, Carol L Cheatham

The American Journal of Clinical Nutrition, Volume 105, Issue 1, January 2017, Pages 32–41, <https://doi-org.libproxy.lib.unc.edu/10.3945/ajcn.116.141390>

Lipids Health Dis. 2018 Mar 9;17(1):43. doi: 10.1186/s12944-018-0693-9.

Omega-6/omega-3 fatty acid intake of children and older adults in the U.S.: dietary intake in comparison to current dietary recommendations and the Healthy Eating Index.

Sheppard KW¹, Cheatham CL^{2,3}.